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EXAMINER	
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,450	LU, XIN	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7 and 9-45* is/are pending in the application.

4a) Of the above claim(s) *11-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/05,10/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 5 May 2008 have been entered. Claims 2 – 7 and 9 – 45 are pending.

Election/Restrictions

2. Applicant's election of Group 1 in the reply filed on 5 May 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 11 – 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5 May 2008.

4. Claims 2 – 7 and 9 – 10 are under examination and will be searched to the extent that they encompass contacting a sample with an agent which binds a polypeptide.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

6. The disclosure is objected to because of the following informalities:

At pp. 16 - 17, the specification recites nucleic acid sequence which do not have sequence identifiers as required by the sequence rules (37 CFR 1.821 - 1.825). A substitute sequence listing may be required if the sequences listed on these pages do not already have SEQ ID NOs. See 37 CFR 1.821 - 1.825 and MPEP §§ 2420—2426 for more detailed instructions on compliance with these rules.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 – 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "stringent hybridisation conditions" in claim 3 is a relative term which renders the claim indefinite. The term "stringent hybridisation conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The skilled artisan could not determine the degree of stringency required. Additionally, since hybridization is a dynamic process that depends on a plethora of factors including but not limited to temperature, ionic strength, presence of agents such as dextran sulfate, and washing conditions, merely reciting "high stringency" or "low stringency" would be insufficient to overcome this rejection.

Claim 4 is confusing and indefinite because it recites the phrase "said nucleic acid" in reference to claim 3. However claim 3 includes multiple nucleic acids: those represented by SEQ ID NO:8 and 9, as well as nucleic acids which hybridize to same. It is unclear which molecule "said nucleic acid" refers to. In order to clarify this issue, it is recommended that applicant amend claim 3 so that one of the molecules in that claim is referred to as "a polynucleotide" rather than a nucleic acid. Such an amendment would clarify which product "said nucleic acid" refers to.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 – 7 and 9 – 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting polypeptides with the sequence of either SEQ ID NO:10 or 11 by contacting samples containing these polypeptides with antibodies, does not reasonably provide enablement for detection of any and all polypeptides as broadly encompassed by claim 2 or for methods of detecting with any and all agents which bind to the polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Here, the nature of the invention is complex. The claims are considerably broader than what is disclosed in the specification, and broader than what could be enabled in the absence of undue experimentation. The specification discloses two proteins, SEQ ID NO:10 and 11. The examiner concedes it is within the skill of the artisan to detect either of these in samples by contacting the samples with antibodies raised against these sequences and measuring the degree of binding. The specification discloses that animals which lack ASPP2 protein (SEQ ID NO:11) could be a model for certain forms of cancer (p. 20 for example). The prior art recognizes that ASPP1 (SEQ ID NO:10) expression is decreased in certain cancers (see Samuels-Lev et al., 2001, cited on IDS filed 6 April 2005). Thus detection of the proteins of SEQ ID NO:10 and 11 is useful. However, what is not enabled is the methods of detecting any and all protein variants. Claims 2 and 3 encompass detection of polypeptides which are encoded by nucleic acids that hybridize to SEQ ID NO:8 and 9 (which encode SEQ ID NO:10 and 11). There is no requirement that any particular region of SEQ ID NO:10 or 11 be present in the detected polypeptide. Given the genetic code, nucleic acids which hybridize to SEQ ID NO:8 or 9 could encode entirely different proteins; there could even be a stop codon within the first codons. The nucleic acids would still hybridize and could be as much as 99% identical, but the resultant proteins could be quite different in sequence. The specification fails to disclose to the skilled artisan how to use a method of detecting a protein other than SEQ ID NO:10 or 11. Alberts (1994. Molecular Biology of the Cell, pp. 104 – 111) teaches that the shape of a protein determines its function (p. 111). Proteins which are of different sequence, and therefore different shape and function, from either SEQ ID NO:10 or 11 would not be expected to have the same expression pattern or function as these two proteins. Thus the artisan would have to determine, on his or her own, what methods of detecting these variants could be used for. The same logic applies to claim 4, which can be construed as encompassing detection of proteins encoded by nucleic acids that hybridize to SEQ ID NO:8 or 9, and to claim 5, which

encompasses methods of detecting any and all protein variants, which require no particular degree of sequence identity to SEQ ID NO:10 or 11.

The specification also does not enable the full scope of "an agent which binds said polypeptide" as recited in claim 2 part (ii). The examiner concedes it is within the skill of the artisan to make an antibody, as recited in claim 6, to a given protein sequence. However, the term "agent which binds said polypeptide" is unlimited by structure. The specification fails to disclose to the artisan the full scope of the agents, and does not teach the public which structures are necessary for binding to the protein. Thus in order to make the full scope of the starting materials required for the methods of claims 2 – 5, the artisan would have to determine, on his or her own, what structures are required. The specification discloses no examples of such agents other than antibodies, and fails to provide sufficient guidance as to how to make the structures. The claims are akin to a single means claim, i.e., where a means recitation does not appear in combination with another recited element of means and is subject to an undue breadth rejection under 35 USC 112, first paragraph because the specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a).

Given the breadth of the claims, and the lack of disclosure and working examples commensurate in scope with the full breadth of the claims, the skilled artisan would have to resort to a very large degree of experimentation in order to practice the entire scope of the claimed methods. Because there is not sufficient guidance as to how to make and use the full scope of the invention, the very large degree of experimentation required would be undue.

9. Claims 2 – 7 and 9 – 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The starting materials required for the methods of claims 2 - 3 and 5 have not been fully described by the specification. Specifically, while the specification discloses the nucleic acid sequences of SEQ ID NO:8 and 9, and the protein sequences of SEQ ID NO:10 and 11, the specification fails to disclose the sequences of any and all proteins encoded by nucleic acids which hybridize to SEQ ID NO:8 and 9, and fails to disclose the sequences of proteins which

differ from SEQ ID NO:10 or 11 "by addition, deletion, or substitution of at least one amino acid residue" as recited in claim 5. Since the claims instruct the skilled artisan to contact a sample with an agent that binds to one of these proteins, the proteins themselves must be described in order for methods of detecting them to be considered described.

As mentioned in the rejection under 35 USC 112, first paragraph, for lack of enablement commensurate in scope with the claims, the specification does not describe the structure of proteins which are encoded by nucleic acids that hybridize to SEQ ID NO:8 or 9. Given the specificity of the genetic code, changing just a small percentage of the nucleotides could result in a completely different protein. For example, changing every sixth nucleotide could result in a protein which could be only 50% identical at the amino acid level, but the nucleic acids would still hybridize as they would be about 85% identical. Deletion of a single nucleotide near the beginning of the protein-encoding region would result in a frameshift mutation that would result in a radically different protein, even though the nucleic acids would share almost 100% identity. The specification fails to disclose the structures of these proteins, and does not disclose partial structures common to all members of the genus. Additionally, the specification fails to disclose the structure of any and all protein variants as recited in claim 5. Note that there is no upper limit on the number of amino acid changes, so claims 2 and 5 encompass methods of detecting any possible protein sequence.

Applicant's attention is directed to the newly-released guidelines on interpretation of the written description requirement, available on the internet at http://www.uspto.gov/web/menu/written.pdf. Note particularly example 9 beginning on p. 31 of that document, which is drawn to protein variants. The situation is analogous to that of claims 2 – 3 and 5, which encompass methods of using protein variants that have not been disclosed or sufficiently described in the specification.

Additionally, the specification fails to describe any and all agents which bind a polypeptide, as recited in claim 2 part (ii). While antibodies (recited in claim 6) have been described, the full genus of "agents" has not been described. The specification provides no examples of such agents beyond antibodies, and does not disclose partial structures common to all members of the agents. The skilled artisan could not reasonably conclude, based on the specification, that applicant was in possession of any protein-binding agents other than antibodies, or methods of using such agents. Thus claim 2 is not fully described for this reason as well.

The remaining claims are rejected as they depend from a rejected base or intermediate claim for the reasons described above.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2 – 7 and 9 – 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson (WO 00/52143, published 8 September 2000).

Anderson teaches methods of contacting samples containing neuronal progenitor cells with agents (specifically antibodies) that bind to said cells and measuring the degree of binding. See for example p. 3 third complete paragraph – p. 8 line 3. See also p. 21 - 22 for a more detailed description of the methods of detecting and sorting cells. While the reference does not explicitly teach using antibodies that bind to SEQ ID NO:10 or 11, claims 2 – 3 and 5 are sufficiently broad that they encompass using antibodies that bind to any protein of any sequence. Note in particular instant claim 5 allows for using an agent (or antibody) that binds to "SEQ ID NO:10 or 11 wherein said sequence has been modified by addition deletion, or substitution of at least one amino acid residue" (emphasis added) As there is no upper limit on the number of changes in the polypeptide sequence, the claim encompass detection of any protein of any sequence. Thus the reference by Anderson anticipates claims 2 – 3 and 5. Claim 4 is included in this rejection as it can be construed as being directed to detection of proteins encoded by nucleic acids which hybridize to either SEQ ID NO:8 or 9. Note there is no degree of identity recited at either the nucleic acid level or amino acid level. Furthermore even though the proteins detected by Anderson are completely different from SEQ ID NO:10 and 11, there will be some degree of hybridization between the nucleic acids encoding the proteins detected by Anderson and SEQ ID NO:8 and 9, as all nucleic acids are comprised of G's, which hybridize to C's, and A's, which hybridize to T's. Thus claim 4 is sufficiently broad that it reads on detection of essentially any protein sequence.

Claim 6 is anticipated as Anderson teaches antibodies. Claim 7 is anticipated as the antibodies are monoclonal (see p. 21 3rd paragraph). Claims 9 - 10 are anticipated as the

antibodies have means which enable their detection, specifically they have IgG1 epitopes which allow for binding of secondary antibodies coupled to phycoerythrin, which is a fluorescent marker as recited in claim 10.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 – 4, 6 – 7, and 9 – 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lev-Samuels (Mol. Cell 8:781 – 794, 2001, cited on IDS filed 6 April 2005) in view of Louis (Journal of Neuropathology and Experimental Neurology 53:11 – 21, 1994).

Independent claim 2 and dependent claim 4 can be construed as encompassing methods of detecting proteins encoded by SEQ ID NO:8 and 9 (i.e., the proteins of SEQ ID NO:10 and 11) in certain specific samples. The specification discloses (p. 14) that ASPP1 is the protein of SEQ ID NO:10 and is encoded by SEQ ID NO:8, while ASPP2 is the protein of SEQ ID NO:11 and is encoded by SEQ ID NO:9. Lev-Samuels teaches methods of contacting samples comprising cells with antibodies against ASPP proteins; see for example Figure 4E which shows visual evidence of detection, p. 792 last complete paragraph for description of making monoclonal antibodies that bind to ASPP1 and ASPP2 (note this is on point to claims 6 and 7), and p. 793 second column for description of the protocol of detecting ASPP proteins in cells. The reference teaches methods of using fluorescently-labeled second antibodies (p. 793) for detection, which is on point to claims 9 and 10, as these are means which enable the detection. Lev-Samuels indicates that mRNA encoding ASPP1 and ASPP2 is decreased in many breast cancers that express wild-type p53, suggesting to the artisan of ordinary skill that decreased levels of ASPP1 and ASPP2 protein would be indicative of the presence of cancer in these tissues. The reference by Lev-Samuels teaches every element of claims 2 – 4, 6 – 7, and 9 – 10, except that Lev-Samuels does not explicitly teach performing the detection assay with samples comprising either nerve cells or nerve progenitor cells as recited in claim 2.

Louis teaches that although some types of brain cancer display mutations in p53, many forms of brain cancer do not have such mutations. That is, the cells remain wild-type at the *p53*

locus, even though they are tumor cells; see for example p. 16 second column and p. 17. This indicates to the artisan of ordinary skill that assays to detect p53 mutations in samples from these tumors would not be useful to determine if the tissue is in fact cancerous. Rather, the artisan of ordinary skill would understand that other proteins must be used in any assay to diagnose whether or not tissue suspected of being cancerous is in fact cancerous. However Louis does not explicitly teach methods of detecting ASPP1 or ASPP2, i.e. the proteins of SEQ ID NO:10 and 11.

It would have been obvious to one of ordinary skill in the art to modify the method of Lev-Samuels and use samples comprising neurons (i.e. nerves) rather than other tissue as taught in the Lev-Samuels reference. The motivation to do so would be to determine if a tumor sample suspected of being cancerous is in fact cancerous, and this motivation comes from the references by Lev-Samuels and Louis. Lev-Samuels teaches that mRNA encoding ASPP proteins is decreased in samples from tumors that are wild-type at the p53 locus, and also teaches how to perform the specific steps set forth in claims 2 - 4, 6 - 7, and 9 - 10. Louis indicates that many brain tumor samples are wild-type at the p53 locus, providing the artisan of ordinary skill a reasonable expectation of success in repeating the steps set forth in Lev-Samuels on brain tumor samples. Performing such a modification would provide the artisan of ordinary skill with a method of diagnosing the presence of brain cancer, which would allow for development of appropriate therapeutic strategies.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
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